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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ROSS J. OEHLER
AVENTIS PHARMACEUTICALS INC.
ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,678	BYK ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-12,14-20,22,23,26-28 and 30-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-12,14-20,22,23,26-28 and 30-36* is/are rejected.

7)☐ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 8/23/04.

Claims 8, 13 , 21, 24, 25, and 29 were canceled, and claims 30-36 were added as requested.

Claims 1-7, 9-12, 14-20, 22, 23, 26-28, and 30-36 are pending and under consideration in this Office Action.

An information disclosure statement was received and entered on 8/23/04.

This Action is NON-FINAL due to new grounds of rejection not necessitated by Applicant's amendment.

Priority

Applicant's amendment to the specification is sufficient to establish a priority claim to US Provisional Application No. 60/085845, filed 5/18/98, and French Application number 98/04121, filed 4/2/1998.

Specification

The specification is objected to because the amendment filed 8/23/04, containing a statement of priority is recites "French Application French Application". Deletion of one instance of "French Application" is suggested.

Rejections/Objections Withdrawn

Applicant's amendments were sufficient to overcome the previous rejections under 35 USC 112, second paragraph. Note that new grounds of rejection are presented below.

Applicant's establishment of a priority claim was sufficient to overcome the rejection of claims 1-7, 9-12, 14-20, 22, 23, and 26-28 under 35 US 102(b).

Applicant's amendments were sufficient to overcome the claim objections of record.

Claim Objections

Claim 1 is objected to because it is ungrammatical. The word "with" at page 6, line 5 should be replaced with "wherein". The word "containing" at line 6 of page 6 should be replaced with the word "contains". The word "is" in the phrase "is the site for bonding" in the penultimate line of page 3, should be deleted.

Claim 27 is objected to because it is ungrammatical. The word "comprising" in line 3 should be replaced with the word "comprises".

Claim 28 is objected to because it is ungrammatical in its recitation of "and and". Deletion of one instance of "and" is suggested

Claim 30 is objected to because both instances of "mirystoylphosphatidylethanolamine" are misspelled. The first 'i' and the first 'y' are transposed.

Claim 36 is objected to because it is ungrammatical. The word "comprising" should be replaced with the word "comprises".

Comment

Claim 35 is a "method for inserting a protein into a cell", and recites method steps requiring transfecting the cell with a DNA molecule encoding the protein such that the protein is expressed within the cell. The claim is considered to satisfy 35 USC 112, second paragraph, but it is noted that the preamble would would more accurately reflect the method steps if it was amended to recite a "method for expressing a protein" rather than a "method for inserting a protein".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 10-12, 14-20, 22, 23, 26-28, and 30-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7, 10-12, 14-20, 22, 23, 26-28, and 30-36 are indefinite because it is unclear what is intended by phrases having the general structure "between *X* and *Y* inclusive", e.g. the phrases "between 0 and 3 inclusive", "between 0 and 10 inclusive", "between 0 and 8 inclusive", "between 1 and 8 inclusive", "between 1 and 10 inclusive", and "between 2 and 8 inclusive". See e.g. third and fourth paragraphs of page 3,

paragraphs defining "W'" on page 4, the first three bullets on page 5, and the paragraphs immediately after structures VIII and IX on page 6. Specifically, the simultaneous use of the terms "between" and "inclusive" in these phrases renders the claims indefinite. These phrases specify limits of a range and simultaneously require the range to exclude the limits and to include the limits. Use of the word "between" in this context implies that the range cannot include the limits, while use of the word "inclusive" implies that the range must include the limits. The claims are indefinite because one of skill in the art cannot know if the ranges include the stated limits or not.

These claims are also indefinite because it is unclear what is intended by the descriptions of variable "W'" at page 4, More specifically, these passages contain the characters CHR"', NR"', and R"' wherein each of these characters is followed by a dash with either two vertical lines drawn through it, or a single set of brackets centered on the dash. It is unclear what this notation means. If the intention was to delete the dash, then Applicant is reminded that 37 CFR 1.121 provides the correct format for doing so, i.e. double brackets around the dash.

These claims are also indefinite because, in the description of Rep at page 5, line 1, they state that the terminal nitrogen of general structure VI can be attached to "the atoms X, V, W, or Z of general formula II". However, the descriptions of X, V, W, and Z at page 4 show that X, W, and Z are never single atoms, and that V may be either a N atom or a NR" group. So, there is no proper antecedent basis for "the atoms X, V, W, or Z of general formula II". Also at line 1 of page 4, the claim states that R1 may be bonded to any atom of general formula (II), including Z". This renders the claim

indefinite because "Z" is never an atom, it always includes at least 2 atoms. See general formulas IV and V.

These claims are also indefinite because R", recited in general structure IV at page 4, is never defined by the claims.

Claims 1-4, 6, 7,10-12, 14-20, 22, 23, 26-28, and 30-36 are indefinite because the phrase "between 0 and 10 inclusive" in the last paragraph of page 3 appears to allow q in general formula III to have a value of 0. This in turn means that the group R1 need not be included in the claimed structure. However, the claims subsequently require that there must be one group R1 in the structure (see lines 1 and 2 of page 4), so the claim is self-contradictory.

Claims 10 and 11 are dependent on "any one of claims 1-9". These claims are indefinite to the extent that they depend on claim 8, which was canceled.

Claim 11 is indefinite because it is unclear what are the metes and bounds of "analogous lipopolyamines". It is unclear what lipopolyamines are intended to be excluded or included by the term "analogous". Does "analogous" include any lipopolyamine that can form the cycloamidine groups, or is it limited to some subgenus of such compounds? Deletion of "analogous" is suggested.

Claims 22 and 23 are indefinite because they depend from canceled claim 13.

Claims 30-32 are indefinite because it is unclear what are the intended members of the Markush group. Specifically it is unclear what is intended by the phrase ""a di-stearoyl, or -palmitoyl, -mirystoylphosphatidylethanolamine [sic]". Does Applicant intend "a di-stearoylphosphatidylethanolamine, a palmitoylmyristoylphosphatidyl-

ethanolamine," etc.? Does Applicant intend "a di-stearoyl-, or di-palmitoyl-, or myristoyl-phosphatidylethanolamine," etc.?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 28 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining enablement are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Nature of the invention

Claim 28 is directed to a method of treating a disease in an animal with a protein capable of correcting said disease by administering a compound of claim I combined with a nucleic acid encoding the protein.

Breadth of the claims

In view of the specification at page 1, lines 4-10, the compounds of claim 1 are intended to be cationic lipids. The scope of nucleic acids contemplated is limited to those encoding any protein viewed as capable of treating a disease. A review of the specification indicates that such proteins include the cystic fibrosis transmembrane conductance regulator (CFTR) and dystrophin, for treatment of cystic fibrosis (CF) and muscular dystrophy (MD), respectively. See pages 25 and 26. As such, the claims embrace methods of treating any protein-related disease, including cystic fibrosis and muscular dystrophy, and one must consider several factors including:

-the general state of the art of gene therapy,

-the state of the art of treating diseases using genes suggested in the specification, such as dystrophin and CFTR genes, and

-the use of cationic lipids in gene therapy.

While the specification provides sufficient guidance to reasonably enable the use of cationic lipids for delivery of DNA to cells, the specification provides insufficient guidance to overcome the unpredictability in the art of treating the claimed breadth of diseases by delivery of nucleic acids. As a result, the specification fails to enable claims limited specifically to generic gene therapy methods of treating a wide variety of

diseases, including e.g. cystic fibrosis and muscular dystrophy, as discussed more fully below.

State of the art and Predictability in the art

Gene therapy in general at the time of the invention

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by reviews at the time of the invention. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18: 19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (Nature Review, Genetics 1: 91-99, 2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector

existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. Thus those of the highest skill in the art before, at, and after the time of the invention, felt that the general art of gene therapy was highly unpredictable and could not be practiced with routine success. Indeed at the time of the invention there was no report of successful gene therapy in humans.

Use of cationic lipids in gene therapy

Cationic lipids are non-viral delivery vectors that are being developed to circumvent some of the art recognized problems with viruses, primarily those pertaining to safety. Cationic lipid vehicles offer the advantages of ease of preparation, no replication risk, and generally lower risk of immune responses. However, a review of the prior art and the art subsequent to filing shows that cationic lipids offer poorer efficiency of gene delivery and expression than do the viral vectors that have proved inadequate for the purpose of gene therapy. See e.g. Ross et al (Human Gene Therapy 7: 1781-1790, 1996), Table 2 at page 1783, and first full paragraph of column 2 on page 1783. Nishikawa et al (Human Gene Therapy 12: 861-870, 2001) taught that factors contributing to the poorer efficiency of cationic nonviral gene delivery include attraction of serum proteins and blood cells, and the difficulty in achieving target-specific gene transfer. See abstract, page 861, column 1, lines 9-17, page 862, column 1, lines 7-9, page 864, column 2, second full paragraph. Additional problems include recognition of unmethylated CpG dinucleotides in expression vectors comprising bacterial DNA sequences (see page 865, paragraph bridging columns 1 and 2), release from endosomes prior to lysosomal degradation, poor stability of DNA in the cytoplasm, and

the inhibitory effects of cationic lipids in the nucleus (see 866, column 1 to end.) Romano (2000) also considered the advantages and disadvantages of cationic lipids as delivery vehicles and noted that they did not allow specific targeting, had low transfection efficiency, gave only transient expression, were difficult to use in vivo, and could give rise to immune responses. See Table 1, on page 23, and first full paragraph of column 2 on page 30. As late as 2003, those of skill in the art still concluded that cationic lipids "are currently not efficient enough to be clinically viable" (Miller (Curr. Med. Chem. 10)14): 1195-1211, 2003)), see abstract, and "are still far from being viable alternatives to the use of viral vectors in gene therapy" (Pedroso de Lima et al (Curr. Med. Chem. 10)14): 1212-1231, 2003)).

Gene therapy of Muscular Dystrophy

The state of the art of gene therapy of DMD is set forth by Karpati and Acsadi (Clin. Invest. Med. 17(5): 499-509, 1994) who teach that several unanswered questions remain to be addressed prior to development of gene therapy for DMD including determining the structure of the dystrophin cDNA to introduce; what type of promoter to use; the method of gene targeting; the required duration of gene expression; and the appropriate route of delivery. See Table 3 at page 501, column 2. Pertinent to the issues of delivery, targeting, and expression, the authors point out that because of the multinucleate nature of muscle cells, and because dystrophin is deposited near the nucleus where its message was expressed, the majority of myonuclei should acquire a normal allele if most of the muscle fiber is to be covered by dystrophin. However, because muscle fibers are surrounded by a well-developed extracellular matrix, efficient

gene delivery is problematic. See page 501, column 1, lines 5-12 and 30-32. With respect to gene delivery systems, the authors teach that a variety of techniques including cationic liposomes have not produced acceptable results *in vivo*. See page 502, column 2, items a-c. Karpati and Acsadi also discuss problems associated with expression of delivered genes, citing degradation of the delivered nucleic acid, promoter silencing, mRNA instability, or destruction of the transfected cell by host immune response. See page 504, paragraph bridging columns 1 and 2. Thus, those of the highest level of skill in the art of therapeutic use of dystrophin at the time the invention was essentially echoed the concerns of Verma, Anderson, Somia, and Romano, above regarding the unpredictable nature of gene therapy and the technical difficulties regarding delivery and expression of therapeutic genes.

Gene therapy of Cystic Fibrosis

The state of the art of CF gene therapy at the time of the invention is set forth by several authors. The example of CF shows why gene therapy must be tailored to fit specific diseases on a case by case basis, and why no single delivery method or composition will be effective to treat all diseases. For example, one of the most important barriers to gene therapy of CF is the lack of information regarding the appropriate target cells for gene delivery. Rosenfeld and Collins (Chest 109:241-252, 1996) teach that it is unclear exactly which cells should receive [gene therapy]", stating that "[t]he difficulty in determining which cells to target relates to an inability to draw parallels between the normal pattern of CFTR expression and the development of CF in lung disease. In normal individuals, the surface epithelium of small airways expresses

very low levels of CFTR, while the submucosal glands found exclusively in large airways express much higher levels. In contrast, in CF, the most important pathologic consequences occur first in the small airways with alveolar damage as a consequence. Little if any clinically significant disease ever occurs where the submucosal glands are found." Boucher (TIG 12(3): 81-84, 1996) notes that this issue is relevant to strategies for vector delivery because while the superficial epithelium of airways can be reached by lumenal vector delivery, the submucosal glands may require systemic administration. See page 1 of reprint, column 2, last sentence of first full paragraph. Rosenecker (Eur. J. Med. 23(3): 149-156, 3/1998) teaches that "[t]opical administration of gene transfer vectors to airways is impeded by surface fluid, mucus plugging the airway lumen, and the ciliated apical surface of epithelial cells" and that the submucosal glands are inaccessible for topically applied formulations. Thus systemic delivery via the blood stream is indicated. See page 152, column 2, lines 1-15 of second full paragraph. Thus, at the time of the invention, those of skill in the art were uncertain as to which cells should be considered targets for CF gene therapy, and what route of delivery would lead to success, assuming the art-recognized problems relating to gene expression after delivery could be solved.

The situation in CF gene therapy is further complicated by an incomplete understanding of the pathophysiology of the disease. Briefly, the molecular problem responsible for CF is a defect in a chloride ion transporter known as CFTR. One hypothetical explanation for the progress of the disease depends on a failure to transport chloride ions, leading to abnormal absorption of sodium ions by the epithelium.

This leads to dehydration and thickening of the mucus in the lungs, which in turn leads to a variety of pathophysiological outcomes including inflammation, repeated infections, and decreasing pulmonary function. Alternatively, the defect in CFTR could somehow affect the actual composition of mucus in the lung, resulting in the recognized pathologies. See Wilson (1995) paragraph bridging pages 2547 and 2548. Thus a primary focus of treatment is the restoration of chloride ion transport. Boucher (1999) teaches that it is likely that the percentage of epithelial cells requiring functional correction to restore normal chloride ion transfer *in vivo* may well exceed 10%, and advises that the simplest strategy to assure efficacy is to mimic the normal pattern of *in vivo* expression by achieving gene expression in 100% of lung epithelial cells. See paragraph bridging pages 441 and 442, page 442 column 1, lines 25-30, and 42- 45. Boucher concludes that a one or two order of magnitude increase in *in vivo* gene transfer efficiency, above that observed in clinical trials, will be required for therapeutic relevance in CF treatment. See page 444, column 2, first sentence of second full paragraph. The state of the art at the time of the invention provided no means to achieve this level of delivery, Verma, Anderson, Somia and Romano, above. Clinical studies have shown success in partially correcting chloride ion transport, however Alton and Geddes (1997) teach that it is unknown whether the chloride or sodium defect associated with CF is the more important error to correct, and that the degree of correction needed for clinical benefit of these defects is unknown. See page 45, lines 7-10 of first full paragraph. Furthermore, Davies (1998) teaches that if normalization of sodium ion transport is required for therapeutic effect, then the levels of gene transfer

observed to date will be inadequate because correction of sodium ion transport has not been achieved in the majority of preclinical and clinical studies. See page 294, column 2, lines 22-28. Rosenfeld (1996) indicates that although restoration of chloride conductance in monolayer cells is achieved by transfection of 5-7% of the cells, normalization of sodium ion reabsorption will require transfection of a much higher percentage of cells. See page 243, column 1, lines 15-18. For all these reasons it was apparent at the time of the invention that the practice of gene therapy of CF was highly unpredictable, and that the state of the art could not support gene therapy of CF. Shortly after the application was filed, Boucher (1999) summarized the state of the art by stating that "despite an impressive amount of research in this area, there is little evidence to suggest that an effective gene transfer approach for the treatment of CF lung disease is imminent."

Guidance and Examples in the specification

Against this background, the specification teaches no working examples of therapeutic delivery of any gene to any patient. Further, the specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense to target cells or tissue in vivo at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims. The cationic lipids of the invention are used to deliver to mice non-therapeutic nucleic acids by intravenous and intramuscular routes, but transfection efficiency is no better than that observed in the prior art for a cationic lipid or naked DNA, respectively. See Figures 7 and 8. For this reason, absent further guidance in the specification, one

of skill in the art would not expect to improve on the results achieved in the prior art which those of skill in the art have judged to be inadequate. However, the specification provides no further guidance for any gene therapy beyond that which was available in the prior art, except for the invention of new cationic lipids. As discussed above (see Verma, Anderson, Somia, and Romano above), the art of gene therapy generally is highly unpredictable and scientifically immature, particularly as shown by the specific examples of DMD and CF gene therapy, such that enablement of gene therapies must generally be considered on a case by case basis with special attention paid to the nature of disease, the therapeutic gene, expression construct, the nature of the vector, and the mode of delivery. The instant specification does not address these issues for specific diseases.

In view of the breadth of diseases embraced by the claims, the state of the art, the unpredictability in the art as assessed by those of the highest level of skill, the lack of any working example of therapy in the specification, and the failure to provide the guidance that is lacking in the prior art, one of skill in the art could not practice the invention as broadly claimed without undue experimentation.

Response to Arguments

Applicant's arguments filed 8/23/04 have been fully considered but they are not persuasive.

At page 32 of the response, Applicant argues that gene therapy is enable because the USPTO has issued since 1992 approximately 209 patents with the phrase

"gene therapy" in the title, some of which were issued prior to the effective filing date of the instant application. This is unpersuasive because the titles of patents are not claims, and do not necessarily reflect the enablement of the claimed subject matter. Applicant notes in particular US patents 5,399,346, to Anderson et al , 5,645,829 to Shockey et al, and 5,821,235 to Henning et al, and concludes that the PTO has clearly admitted by issuing these patents that at the of the invention gene therapy methods were known that were novel useful and enabled. Applicant is reminded that each Application is considered on its own merits. The argument is unpersuasive because it fails to address how any publication, patent or otherwise, provides any evidence that the specific subject matter claimed herein is enabled. It does not specifically address the arguments set forth in the enablement requirement, as they relate to factors set forth in *In re Wands*, or to specific examples of diseases set forth in the specification such as CF and DMD. Furthermore, it is noted that the Henning patent has no claim to any method of treating any disease, and the claims of the Shockey patent are much narrower than the instant claims, being limited by Jepson language to improvements in existing methods. The position of the Office is not that there were no existing gene therapy methods at the time of the invention. The Office's position is that claim 28 is not limited to any specific gene therapy method and broadly embraces treatment of any disease that could conceivably be corrected by a protein, and the specification does not support a claim of this breadth for the reasons set forth in the rejection.

At page 33 of the response, Applicant argues that non-viral vectors are adequate for the purpose of gene therapy, relying for support on six different publications showing

in vivo protein delivery by use of cationic lipids. The Alino (1994), Canonico(1994), Nabel (1990), and Zhu (1993) references do not exemplify treatment of any disease. Instead these references exemplify successful expression of delivered genes in vivo, as was indicated in the rejection to be enabled. The Sorscher (1994) reference is a description of a gene therapy clinical trial for CF. The relevance of this reference is clear from the enablement rejection above that cites numerous references published after 1994 that describe in detail why no gene therapy treatment of CF was enabled at the time the invention was filed. Applicant's response provides no evidence to the contrary, particularly inasmuch as the Sorscher reference only describes a clinical trial and provides no results. As a result, nothing in the Alino (1994), Canonico(1994), Nabel (1990), Zhu (1993) or Sorscher (1994) references provides supports the position that the claims are enabled. The Wilson reference discloses a transient improvement in hypercholesterolemia by targeted delivery of LDL receptor genes to hepatocytes using a protein /DNA complex. This paper provides evidence for enablement of a very narrow method of transient therapy by means of protein-targeted delivery, and does not teach the use cationic lipids. As such, the paper does not provide evidence that would enable the invention as broadly claimed, i.e. treatment of any disease that can be treated by providing a protein, using a cationic lipid delivery composition, by any route of delivery. For these reasons the rejection is maintained.

Conclusion

No claim is allowed. Claim 9 is objected because it depends from a rejected claim, but would be allowable if rewritten in independent form, i.e. "A compound having a formula selected from the group consisting of [structures of compounds 1-6]."

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.